Hepatitis B and D:
Fun Parts of the Liver's Alphabet

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Hepatitis B Virus (HBV) Virology

- Hepadnavirus- partial ds-DNA virus
- Outer lipoprotein envelope
- Inner core of nucleocapsid proteins
- Viral polymerase using reverse transcription
- Massively overproduce envelope proteins (HBsAg)

HBV Virology

- Intact virion diameter- 42 nm
- Envelope- S (HBsAg), L, and M proteins
  -L protein- role in hepatocyte binding
- Nucleocapsid Core- 27nm diameter
  -180 copies of core protein (HBcAg)
- Viral Genome- 3.2kb minus DNA strand
  – variable plus DNA strand
  – Polymerase with RT activity

HBV Virology

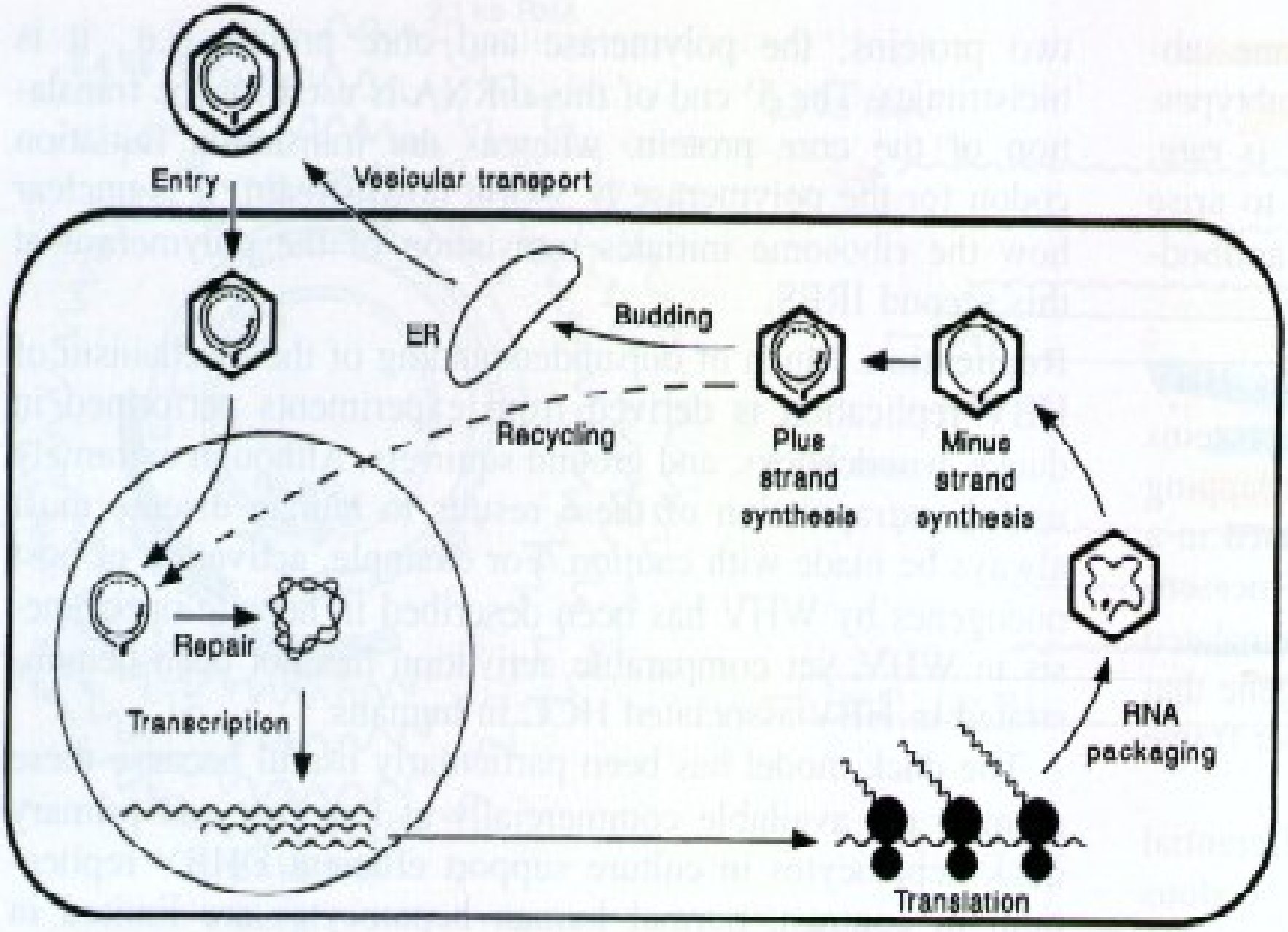
- Serologic Subtypes- adw, ayw, adr, ayr
  - -Different geographic distributions
  - -Unclear clinical significance
- Subtype infection is cross-protective

HBV Genomic activity

- Four major proteins encoded- surface, core, X proteins, and polymerase
- Overlapping reading frames
- mRNA’s differentially spliced
- HBeAg- represents signal sequence on pre-core protein precursor
  - marker for active viral replication

HBV Replication

- Viral binding, entry, and uncoating
- Complete DS DNA synthesis in nucleus
- RNA and protein production
- Encapsulation of genomic RNA
- Polymerase production of DNA strands
- Envelopment and release


Entry
Vesicular transport
ER
Budding
Recycling
Plus strand synthesis
Minus strand synthesis
Repair
Transcription
RNA packaging
Translation

HBV Epidemiology

- Chronic HBV- 5% of world's population
- High Prevalence- (8-15%) Asia, Middle East, parts of S. America
- Intermediate- (2-7%) Japan, S. America, and ***Alaska*** (6.4%)
- Low-(<2%) USA, Canada, Western Europe

U.S. HBV Epidemiology

- 1-1.25 million have chronic infections
- Males > females
- Male peak prevalence- 10-30yo
- Blacks (14%) > whites (2-3%)
- children at much higher risk of developing chronic disease

HBV Transmission

- Blood or blood products
  - transfusion risk -1/50,000 per unit
- IV drug use
- Sexual Contact
- Peri-natal transmission
- Iatrogenic health care worker exposure
  - needle sticks

HBV Pathogenesis

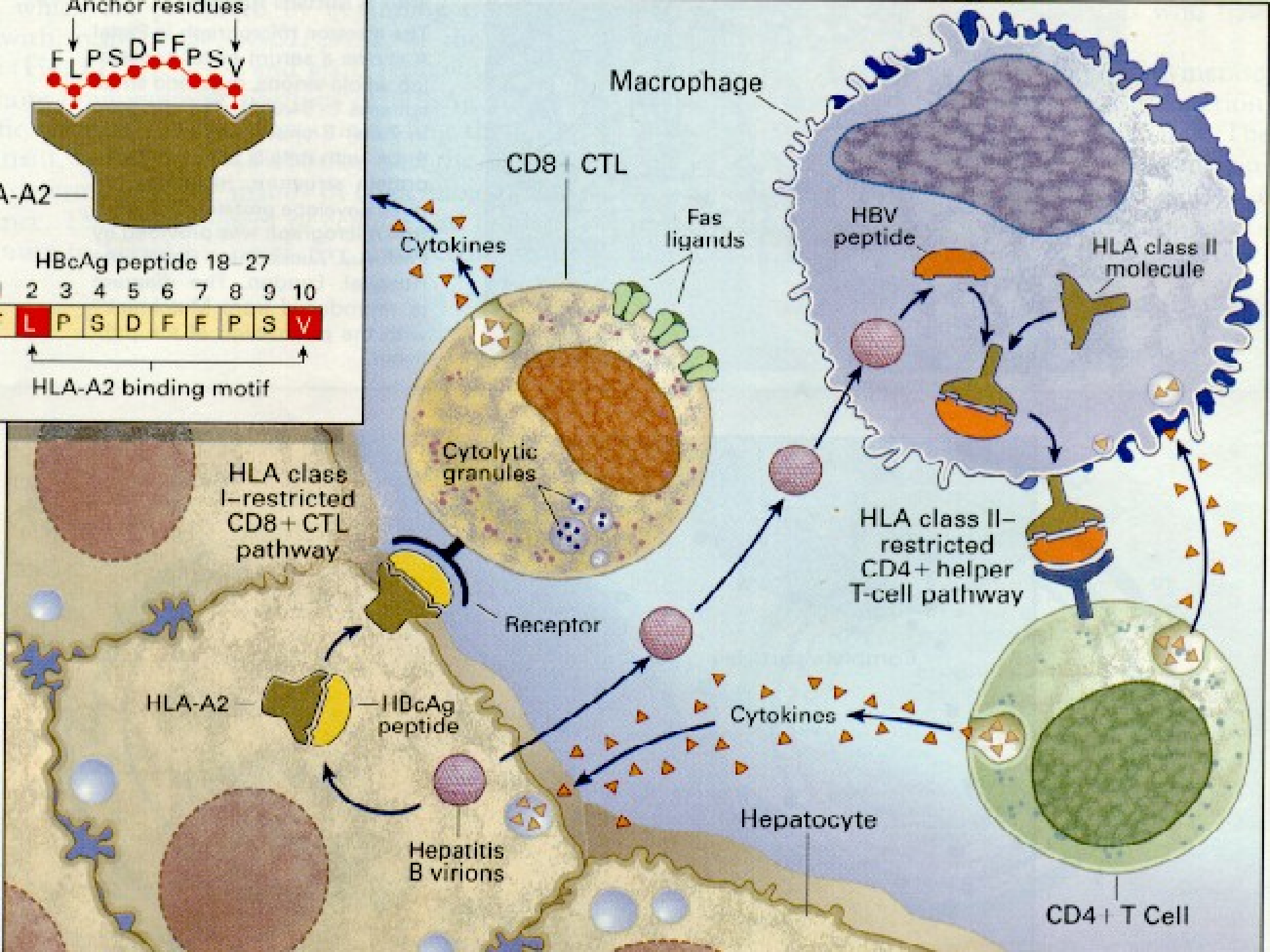
- No direct cytopathic effect

- Immune response- CMI and humoral

  -Cytokine Mediators- primary importance

  -IFN-*g* and TNF-*a* - eliminate nucleocapsids and destabilize viral RNA

  -Cytotoxic lymphocytes- secondary role


Anchor residues
F L P S D F F P S V
A-A2
HBcAg peptide 18–27
2 3 4 5 6 7 8 9 10
L P S D F F P S V
HLA-A2 binding motif
Macrophage
CD8+ CTL
Cytokines
Fas ligands
HBV peptide
HLA class II molecule
Cytolytic granules
HLA class I–restricted CD8+ CTL pathway
HLA class II–restricted CD4+ helper T-cell pathway
Receptor
HLA-A2
HBcAg peptide
Cytokines
Hepatocyte
Hepatitis B virions
CD4+ T Cell

HBV Manifestations: Acute Infection

- Incubation- 60-180 days
- Symptoms- asymptomatic to fulminant hepatic failure
  - arthralgias, fatigue, jaundice, rashes
- Pro-dromal phase correlates to LAE changes
- ALT>=AST:: in 500-1000's
- Total Bilirubin- usually 5-10 mg/dl

HBV Chronic Infection

- Defined as persistent Viral activity for more than 6 Months.
- ALT falls to lower abnormal levels
- Associations- PAN, HCC, Cirrhosis, MPGN, Guillain Barre Syndrome

Serologic Evaluation

- HBsAg/HBcAg- confirms active infection
- HBsAb- marker of resolution
- HBcAb- may persist for life
  - suggests prior infection
- HBeAg- correlated with viral replication
  - marker for infectivity risk
- HBeAb-typically suggests no further replication
- Viral Load- DNA/PCR being used more frequently

HBV Therapies
Interferon-alpha

- IFN-a- first large trial (169 pts) in 1990 compared 5mu/day, 1mu/day, Prednisone plus 1mu/day, or placebo

  -5mu/day group- 37% response rate

  -1mu/day- 17% placebo- 7%

- Meta-Analysis- (837 pts, 15 RCT's)
  - 5-10mu/3x weekly--> 35-40% response rate
  - 3 months is equivalent to 6 months

Perillo.*NEJM*. 232:1990

Wong. *Ann Int Med*.1

HBV Interferon Therapy

- Indications-
  - Persistent AST/ALT elevations for 6 months
  - Detectable HBsAg, DNA, and HBeAg
  - Active inflammation
- Contra-indications-
  - De-compensated cirrhosis
  - Concurrent Autoimmune disease
  - Active substance abuse
  - Poor psychiatric disease control

HBV Interferon Therapy

- Predictors of Response-
  - High Serum AST/ALT
  - Low HBV DNA levels
  - Short Duration of Infection
  - Histologic picture of active hepatitis
  - HIV negativity

HBV Interferon Therapy

- Current Dosing- 5mu/day or 10mu/ 3x wk
  - 16 Week Therapy is Standard
- Follow-up- Check LFT's at 2-4 wk intervals
  HBV serology at start, end of tx,
  and 6 months after tx
- AST/ALT increase- suggests response
  - thought to be clearance of infected hepatocytes

HBV IFN-a Responses

- Transient- mild decrease in AST/ALT and HBV DNA
  -Levels return to pre-tx levels
- Sustained- (40%) loss of viral replication
  -60-70% have AST/ALT flare during tx, but then normalize
  -HBsAG remains positive
- Complete- Same as Sustained, except HBsAG is lost

IFN-a Side Effects

- Constitutional
  - Flu-like sx -Malaise/Fatigue -Anorexia
  - N/V -Myalgias -Wt Loss
- Hematologic- BM Suppression
  - common, but usually insignificant
- Neuropsychiatric- (15% of pt's)
  - Depression, irritability
- Autoimmune- Thyroid disease, auto-Ab's (50%)

HBV Therapy: RT Inhibitors

- Lamivudine- HIV RT inhibitor found to have HBV activity (nucleoside analog)
  - at least 100mg/day dosing for 3 months
  - 95%+ circulating HBV DNA reduction
  - HBV DNA returns after therapy ends
- 1 Year Trials-
  - 96% had complete DNA clearance
  - Viremia usually returned after cessation
  - 16% develop resistant mutant strains

Lee, *NEJM*,337:19

HBV Therapy: Other Agents

- IFN-beta and gamma-
  - not well studied alone
- HSV Antivirals- nucleoside analogs
  - Gancyclovir-moderate DNA lowering
  - Famciclovir-strong HBV DNA lowering
- Fialuridine- strong inhibition, but toxic

HBV Therapy: Liver Transplantation

- 1 year survival <50% (chronic HBV)
  - recurrent HBV infection major factor
- Fulminant Acute HBV infection-

  lower risk of recurrence and

  better overall survival
- Post-op HBIG- plays important role in preventing recurrence
- Nucleoside Analogs- developing role
  - lamivudine, famciclovir

Hepatitis D Virus

- First described in 1977
- Small defective RNA virus similar to several plant viruses
- Requires “helper” virus to provide encapsulation

HDV Virology

- 36nm particle- RNA and Delta Antigen
  - Delta Ag- large and small varieties
    -Large Ag- suppress replication and

      promotes viral assembly with HBsAg.
    -Small Ag- promotes replication
- Single strand RNA
- Replication limited to Liver, but HBV needed to allow cell-cell spread

HDV Epidemiology

- 15 million infected wordwide
- High prevalence- Italy, Eastern Europe, Amazon Basin, Pacific Islands
- 1.4-8% U.S. prevalence (blood donors)
- IVDU- 20-50%
- can be sexually transmitted

HDV Transmission

- Similar to HBV
- Percutaneous routes most efficient
- Co-infection with HBV and HIV common
- Sexual transmission is less efficient than HBV
  - -33% of IVDU's sex partners in one study
- Perinatal transmission rare

Leon, *J Clin Micro Infect Dis*,7:1988

HDV Pathogenesis

- Directly Cytotoxic
- HDV replication intermediates- may interfere with hepatocellular protein sorting
- Immune response- may also play role
  - auto-antibodies are commonly found

HDV Manifestations:

- Co-infection- biphasic AST/ALT increase
  - atypical for HBV alone
  - transient HBV/HDV-->HDV has little impact on development of chronic infection
- Super-infection- established chronic HBV
  - results in progressive disease in 90%
- Chronic- increased AST/ALT in chronic HBV
  - early cirrhosis

HDV Serology

- Anti-HDV Ab- most commonly used
  - becomes positive late in course
- HDV RNA- Research basis only
- HDV Ag- persists into symptom phase only in 20% of pt's
  - only transient
- HBsAg- necessary marker to have HDV activity

HDV Therapies

- Low dose IFN-a- RCT for 6-12 months showed no lasting benefit
- Italian Trial- 9mu/3x wk for 12 months
  - 36% remission
- Recent therapy review suggests 15-25% sustained response at 10mu/3x week

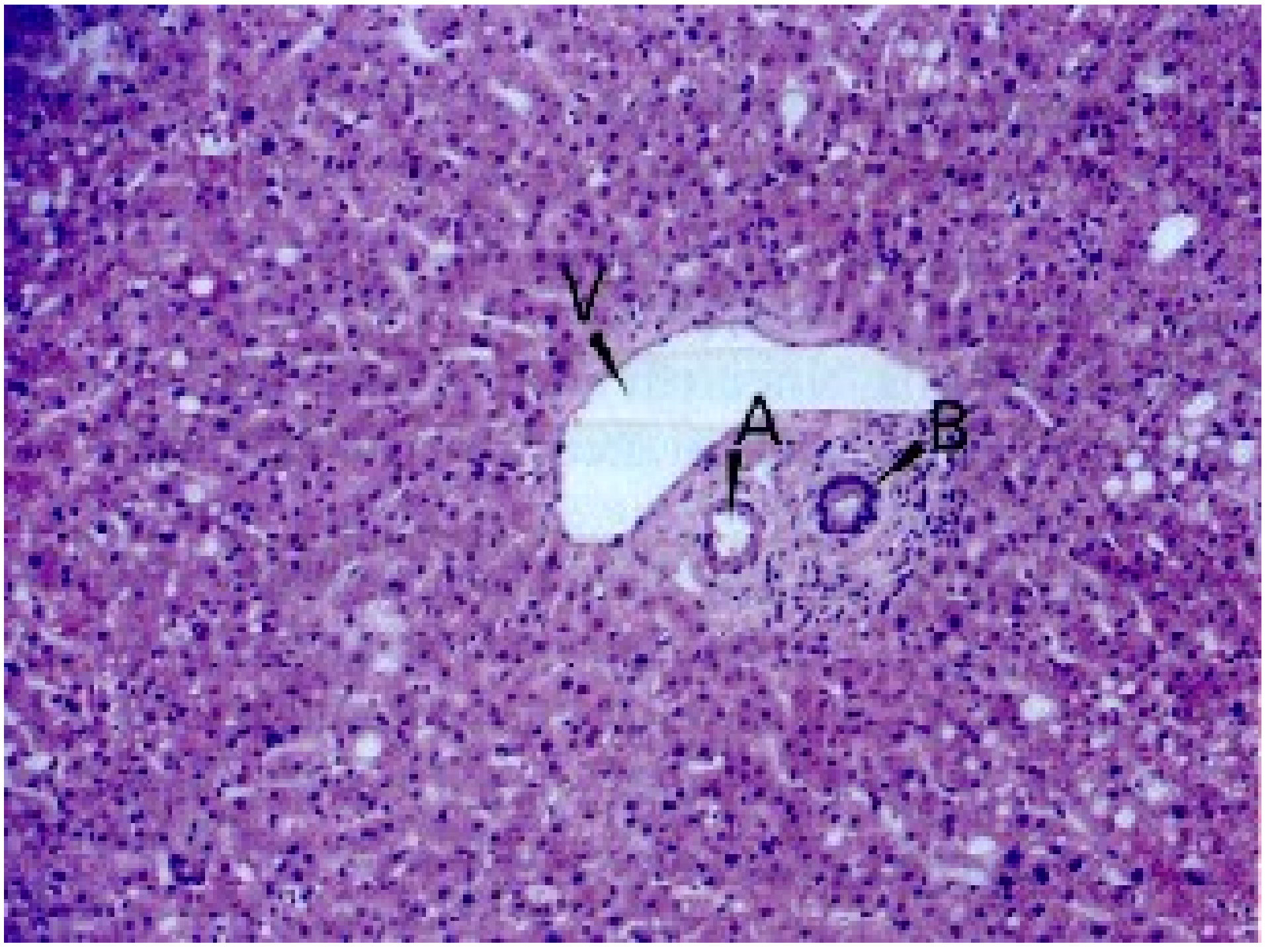
Farci.*NEJM*.330:1994

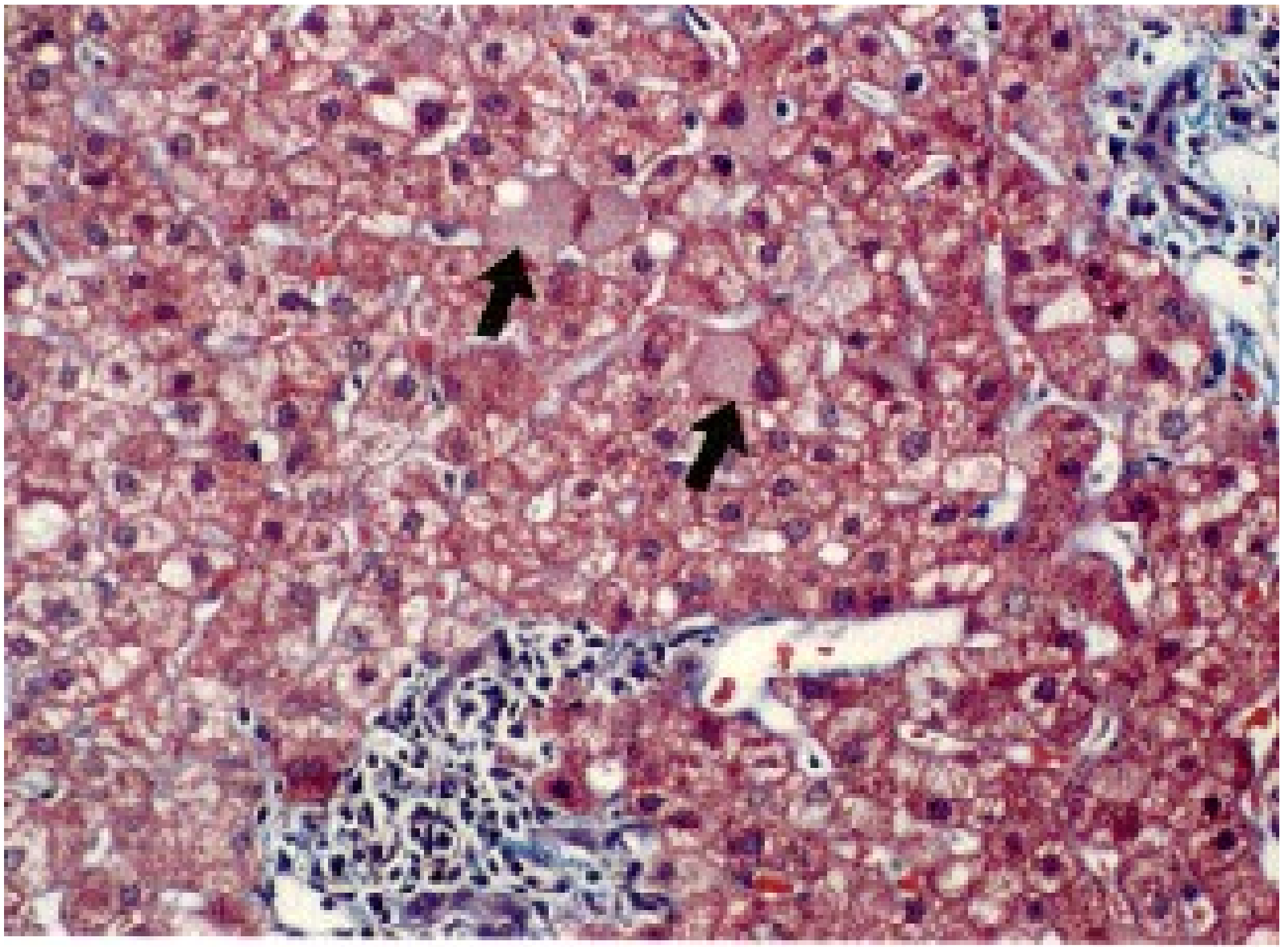
HDV Therapies: Liver Transplantation

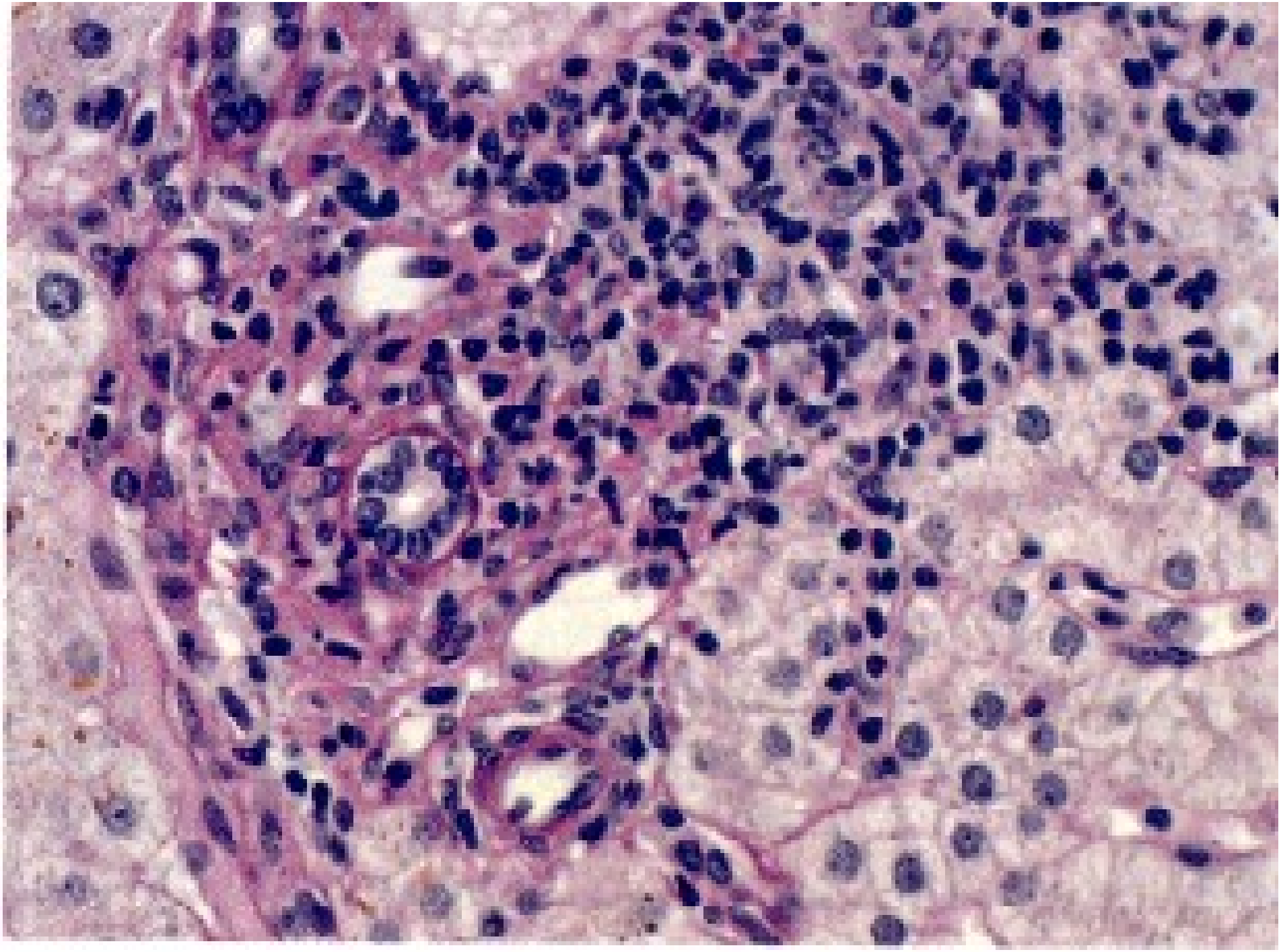
- De-compensated Cirrhosis or Fulminant Hepatic Failure
- Lower HBV re-infection rate (32% vs. 67%)
  - secondary to HDV inhibition of HBV replication
- Better Survival than HBV alone
  - 88% 3yr survival for HDV -44% 3yr for HBV
- HBIG- decreased HBV re-infection and improves survival

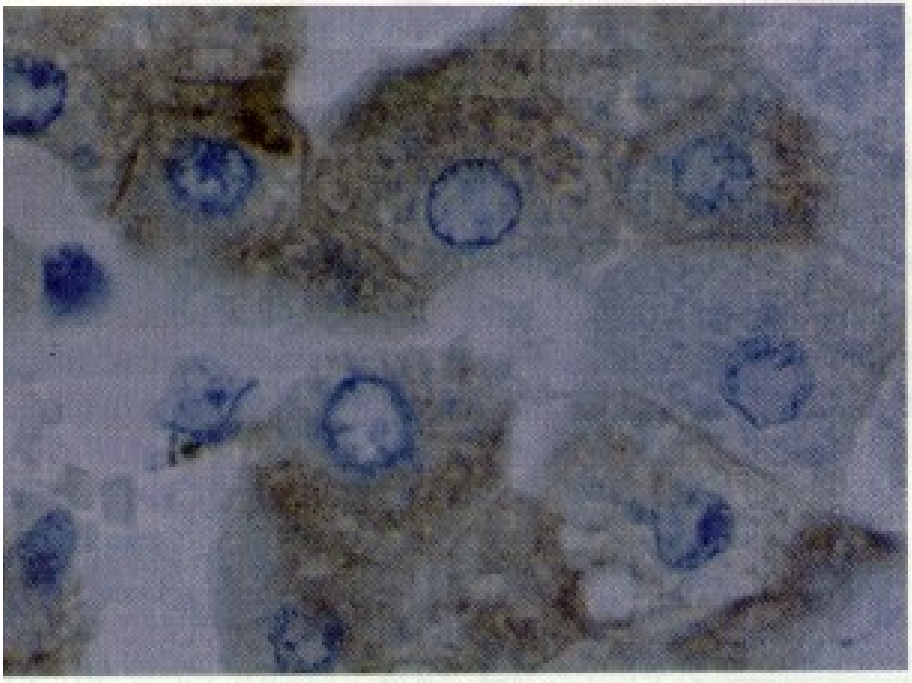
Conclusions

- HBV and HDV are chronic and potentially lethal viral agents
- No good therapy exists, with IFN being the best choice.
  - Less than 50% respond
- Prevention and vaccines are key


V
A
B







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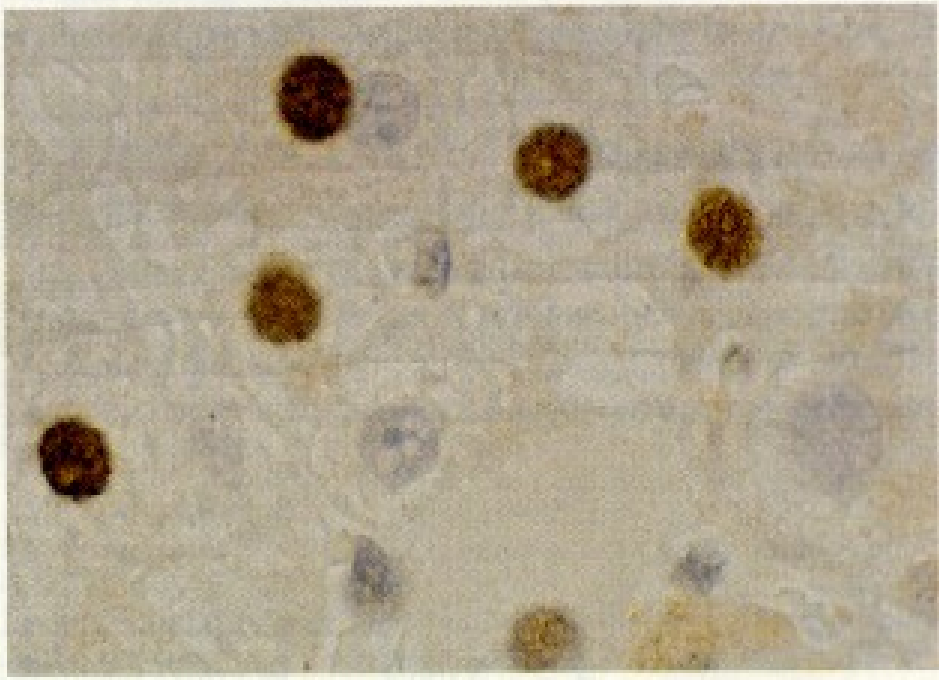

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